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(54) Title: AMORPHOUS TORASEMIDE MODIFICATION

(57) Abstract: The present invention relates to an amorphous torasemide modification, to a process for the preparation thereof, to its use as a raw material for the preparation of pharmaceutically acceptable salts of torasemide, to pharmaceutical forms containing this amorphous torasemide modification as well as to its use as a diuretic.

AMORPHOUS TORASEMIDE MODIFICATION

International Patent Classification: C 07 D 213/70; A 61 K 31/44

The present invention relates to an amorphous modification of *N*-(1-methylethyl aminocarbonyl)-4-(3-methyl-phenylamino)-3-pyridinesulfonamide (in the further text of the application designated by its generic name "torasemide"), to a process for its preparation, to its use as a raw material for pharmaceutically acceptable salts of torasemide, to pharmaceutical forms containing the said amorphous torasemide modification as the active ingredient as well as to its use as diuretic.

Torasemide is a new potential diuretic in the class of the so-called "loop diuretics", which is described in DE patent 25 16 025 (Example 71). Structurally, it entirely differs from diuretics of the same class such as furosemide, bumetanide and azosemide. In addition to diuretic properties it also possesses antihypertension properties.

As a diuretic of Henle's loop it is useful as an agent for preventing heart or heart tissue damages caused by metabolic or ionic abnormalities associated with ischemia, in the treatment of thrombosis, angina pectoris, asthma, hypertension, nephroedema, pulmonary edema, primary and secondary aldosteronism, Bartter's syndrome, tumours, glaucoma, decreasing of intraocular pressure, acute or chronic bronchitis, in the treatment of cerebral edema caused by trauma, ischemia, concussion of the brain, metastases or epileptic attacks and in the treatment of nasal infections caused by allergens.

The ability of a substance to exist in more than one crystal form is defined as polymorphism and these different crystal forms are named "polymorph modifications" or "polymorphs". In general, polymorphism is caused by the ability of the molecule of a substance to change its conformation or to form different intermolecular or intra-molecular interactions, particularly hydrogen bonds, which is reflected in different

atom arrangements in the crystal lattices of different polymorphs. Polymorphism is found in several organic compounds. Among medicaments polymorphism is found in about 70% of barbiturates, 60% of sulfonamides and 60% of steroids, and about 50% of medicaments of the said classes are not present on the market in their most stable forms (T. Laird, Chemical Development and Scale-up in the Fine Chemical Industry, Principles and Practices, Course Manual, Scientific Update, Wyvern Cottage, 1996).

The different polymorphs of a substance possess different energies of the crystal lattice and, thus, they show different physical properties of the solid state such as form, density, melting point, colour, stability, dissolution rate, milling facility, granulation, compacting etc., which in medicaments may affect the possibility of the preparation of pharmaceutical forms, their stability, dissolution and bioavailability and, consequently, their action.

Polymorphism of medicaments is the object of studies of interdisciplinar expert teams [J. Haleblian, W. McCrone, *J. Pharm. Sci.* **58** (1969) 911; L. Borka, *Pharm. Acta Helv.* **66** (1991) 16; M. Kuhnert-Brandstätter, *Pharmazie* **51** (1996) 443; H. G. Brittain, *J. Pharm. Sci.* **86** (1997) 405; W. H. Streng, DDT **2** (1997) 415; K. Yoshii, *Chem. Pharm. Bull.* **45** (1997) 338, etc.]. A good knowledge of polymorphism represents a precondition for a critical observation of the whole process of medicament development. Thus, at deciding on the production of a pharmaceutical form in solid state and with regard to the dose size, stability, dissolution and anticipated action, it is necessary to determine the existence of all solid state forms (on the market some computer programmes can be found, e.g. »Polymorph« as a module of »Cerius2« programme, MSI Inc., USA) and to determine the physical-chemical properties of each of them. Only on the basis of these determinations the appropriate polymorph can be selected for the development of pharmaceutical formulations of desired properties.

From the great number of such efforts only a few will be mentioned as an example. Thus, Chikaraishi et al. (WO 9626197) protected, in addition to a polimorph form,

also an amorphous form of piretanide as well as processes for preparation thereof. J.-B. Cha et al.. (WO 9857967) protected an amorphous form, a process for the preparation thereof and pharmaceutical formulations of the medicament itraconazole containing this amorphous form; E. Occeli et al. (WO 9000553) protected crystal polimorphs I and II and the amorphs of the medicament rifapentine hydrochloride and hydrobromide. Further, for the new antidiabetic troglitazone G. Om Reddy et al. (US 5,700,820) protected six polimorphs: five crystal polimorphs and one amorphous one. It is known that torasemide can exist in three crystal modifications differing with regard to the parameters of a single cell, which is confirmed by X-ray diffraction on their monocrystals. Modification I with melting point 169°C [*Acta Cryst.*. B**34** (1978), 1304-1310] and modification III with melting point 165°C [HR patent application P980532A (US patent application 09/187046)] crystallize monoclinically in the space group P $2_1/c$ (prisms), while modification II with melting point 162°C crystallizes monoclinically in the space group P 2/n (foils) [*Acta Cryst.* B**34** (1978), 2659-2662].

In addition to the above, US patent 5,914,336 protected the use of a new torasemide polimorph, however, only some of its physical-chemical properties such as melting point, heat of formation, solubility, first band in IR-spectrum, but no X-ray patterns of the powder and monocrystal were stated.

In our further research in the field of torasemide we have surprisingly found an amorphous torasemide modification which has hitherto not been known.

The amorphous torasemide modification has the form of an amorphous voluminous powder, which - in the same way as the powder obtained by the grinding thereof - does not show any diffraction maxima at recording the X-ray powder pattern, which demonstrates the amorphous nature thereof.

In the solution the amorphous modification is identical with other known torasemide modifications, which is evident from NMR and UV spectra. On the other hand, solid state analysis techniques such as differential scanning calorimetry (DSC), X-ray

powder pattern (XRD) and IR spectroscopy reveal the difference in comparison to the known torasemide modifications.

DSC of the amorphous torasemide modification (Fig. 1) shows one exothermic maximum at about 147°C (onset at about 144°C) resulting from decomposition (also evident on the basis of IR spectroscopy and thin-layer chromatography).

The X-ray powder pattern of the amorphous torasemide modification differs from the X-ray powder patterns of the known torasemide modifications and does not show any diffraction maxima, which confirms the amorphous nature (Fig. 2).

The IR spectrum of a sample of the amorphous modification recorded in KBr (Fig. 3) differs from IR spectra of the known torasemide modifications. The amorphous torasemide modification shows characteristic absorption bands at 2900 to 3366 cm^{-1} and at 1400 to 1703 cm^{-1}.

Fig. 1 represents a characteristic thermogram of differential scanning calorimetry (DSC) of the amorphous torasemide modification.

Fig. 2 represents a characteristic X-ray powder pattern of the amorphous torasemide modification.

Fig. 3 represents a characteristic IR spectrum of the amorphous torasemide modification recorded in KBr.

The amorphous torasemide modification according to the present invention can be obtained by dissolving modifications I, II or III or an amorphous torasemide modification or any mixture thereof in water with or without the addition of a base and a subsequent removal of the water and base from such solutions.

The process for the preparation of an amorphous torasemide modification comprises:

(i) the preparation of torasemide polimorph I according to a known process,
(ii) the dissolution of polimorph I in water with or without the addition of a base at a temperature from 5 to 100°C within 5 minutes to 24 hours,
(iii) the filtration of the obtained solution,
(iv) the cooling of the obtained solution at a temperature from -20°C to -70°C,
(v) the removal of water and the base from the frozen solution in order to prepare an amorphous torasemide modification, which is characterized by the following data:
DSC: exothermic maximum at about 147°C (onset at about 144°C) (Fig. 1);
X-ray powder pattern (2 Θ): no diffraction maxima due to the amorphous nature (Fig. 2);
IR-characteristic absorption bands (cm^{-1}): at 2900 to 3366 and at 1400 to 1703 (Fig. 3).

According to a further embodiment of the present invention the process for the preparation of an amorphous torasemide modification also comprises:
(i) the preparation of torasemide polimorph II according to a known process,
(ii) the dissolution of polimorph II in water with or without addition of a base at a temperature from 5 to 100°C within 5 minutes to 24 hours,
(iii) the filtration of the obtained solution,
(iv) the cooling of the obtained solution at a temperature from -20°C to -70°C,
(v) the removal of water and the base from the frozen solution in order to prepare an amorphous torasemide modification, which is characterized by the data represented in the previous process.

According to a further embodiment of the present invention the process for the preparation of an amorphous torasemide modification also comprises:
(i) the preparation of torasemide polimorph III according to a known process,
(ii) the dissolution of polimorph III in water with or without the addition of a base at a temperature from 5 to 100°C within 5 minutes to 24 hours,
(iii) the filtration of the obtained solution,
(iv) the cooling of the obtained solution at a temperature from -20°C to -70°C,

(v) the removal of water and the base from the frozen solution in order to prepare an amorphous torasemide modification, which is characterized by the data represented in the previous process.

According to a further embodiment of the present invention the process for the preparation of an amorphous torasemide modification also comprises:
(i) the preparation of an amorphous torasemide modification according to the process of the present invention,
(ii) the dissolution of the amorphous torasemide modification in water with or without the addition of a base at a temperature from 5 to 100°C within 5 minutes to 24 hours,
(iii) the filtration of the obtained solution,
(iv) the cooling of the obtained solution at a temperature from -20°C to -70°C,
(v) the removal of water and the base from the frozen solution in order to prepare an amorphous torasemide modification, which is characterized by the data represented in the previous process.

According to a further embodiment of the present invention the process for the preparation of an amorphous torasemide modification also comprises:
(i) the preparation of torasemide polimorphs I, II and III according to known processes and the preparation of an amorphous torasemide modification according to the process of the present invention,
(ii) the dissolution of any mixture of the torasemide polimorphs I, II and III or of the amorphous torasemide modification in water with or without the addition of a base at a temperature from 5 to 100°C within 5 minutes to 24 hours,
(iii) the filtration of the obtained solution,
(iv) the cooling of the obtained solution at a temperature from -20°C to -70°C,
(v) the removal of water and the base from the frozen solution in order to prepare an amorphous torasemide modification, which is characterized by the data represented in the previous process .

According to the process of the present invention, an aqueous ammonia solution is used as the base for the preparation of the aforementioned aqueous torasemide solutions.

According to the process of the present invention, lyophilization is used as the method for the removal of the water and the base.

It has been found that by the use of the process of the invention no decomposition of torasemide takes place, i.e. a chemically pure amorphous torasemide modification is obtained (TLC and HPLC).

It has also been found that the amorphous torasemide modification is stable under normal storage conditions, at crushing and compressing, i.e. it does not convert into a crystal modification I, II or III of torasemide.

The amorphous torasemide modification prepared according to the present process can be converted to crystal modifications I, II and II of torasemide by conventional processes, i.e. it may be used as a starting material for the preparation of the known crystal modifications I, II and III of torasemide.

The amorphous torasemide modification prepared according to the present invention can be converted into pharmaceutically acceptable salts of torasemide by means of conventional processes.

The research of the release (USP 24) of the amorphous torasemide modification in water in comparison with the profile of the release of the known crystal torasemide modifications in the same medium has shown its slower release. The amorphous torasemide modification as such is suitable for the preparation of pharmaceutical prepartions having short-term or prolonged actions.

The amorphous torasemide modification prepared according to the process of the present invention is a suitable torasemide form to be used as a diuretic and as an agent for preventing heart or heart tissue damages caused by metabolic or ionic abnormalities associated with ischemia, in the treatment of thrombosis, angina pectoris, asthma, hypertension, nephroedema, pulmonary edema, primary and secondary aldosteronism, Bartter's syndrome, tumours, glaucoma, for decreasing intraocular pressure, acute or chronic bronchitis, in the treatment of cerebral edema caused by trauma, ischemia, concussion of the brain, metastases or epileptic attacks and in the treatment of nasal infections caused by allergens.

The present invention also relates to pharmaceutical forms such as tablets, capsules and injections containing an effective amount of the amorphous torasemide modification as the active ingredient without any additives or combined with one or more pharmaceutically acceptable additives such as sugar, starch, starch derivatives, cellulose, cellulose derivatives, mould release agents, and antiadhesive agents and possibly agents for flowability regulation.

The present invention is illustrated but in no way limited by the following Examples.

Example 1

The crystal modification I of torasemide (3.00 g) prepared according to *Acta Cryst.* B34 (1978) 1304-1310 was suspended in 60 ml of demineralised water at 25°C, 30 drops of an aqueous ammonia solution were added and the obtained solution was stirred at the same temperature for 24 hours and then filtered. Subsequently, the solution was frozen at a temperature of about -70°C, whereupon the water and ammonia were removed by lyophilization.

After isolation from the lyophilization vessel there were obtained 2.87 g of an amorphous torasemide modification; melting point (apparatus for melting point determination: Büchi 535): start of softening at about 80°C, decomposition at about 148°C.

The characteristic IR spectrum of the sample as shown in Fig. 1 was recorded in KBr in the IR-spectrophotometer Nicolet-Magna 760.

The characteristic X-ray powder pattern as shown in Fig. 2 was recorded in the instrument PHILIPS PW3710 under Cu X-rays [$\lambda(CuK\alpha_1) = 1.54046$ Å and $\lambda(CuK\alpha_2) = 1.54439$ Å].

The characteristic DSC curve of the sample as shown in Fig. 3 was recorded in the apparatus Perkin-Elmer DSC7 at a heating rate of 5°C/minute.

Example 2

The crystal modification I of torasemide (0.08 g) prepared according to *Acta Cryst.* B34 (1978) 1304-1310 was dissolved under stirring in 50 ml of demineralised water at a temperature of about 80°C within 3 hours, whereupon the solution was cooled to room temperature and filtered. Subsequently, the solution was frozen at a temperature of about -50°C and the water was removed by lyophilization.

After isolation from the lyophilization vessel there were obtained 0.05 g of an amorphous torasemide modification; melting point (apparatus for melting point determination: Büchi 535): start of softening at about 80°C, decomposition at about 148°C.

The IR spectrum of the thus obtained sample corresponded to the IR spectrum of the new amorphous modification obtained in Example 1.

Example 3

The crystal modification II of torasemide (1.00 g) prepared according to *Acta Cryst.* B34 (1978) 1304-1310 was suspended in 50 ml of demineralised water at 10°C, 10 drops of an aqueous ammonia solution were added and the obtained solution was stirred at the same temperature for 12 hours and then filtered. Subsequently, the solution was frozen at a temperature of about -60°C, whereupon the water and ammonia were removed by lyophilization.

After isolation from the lyophilization vessel there were obtained 0.98 g of an amorphous torasemide modification; melting point (apparatus for melting point determination: Büchi 535): start of softening at about 80°C, decomposition at about 148°C.

The IR spectrum of the thus obtained sample corresponded to the IR spectrum of the new amorphous modification obtained in Example 1.

Example 4

The crystal modification III of torasemide (1.00 g) prepared according to HR patent application P980532A (US patent application 09/187046) was suspended in 50 ml of demineralised water at 20°C, 10 drops of an aqueous ammonia solution were added

and the obtained solution was stirred at the same temperature for 5 hours and then filtered. Subsequently, the solution was frozen at a temperature of about -60°C, whereupon the water and ammonia were removed by lyophilization.

After isolation from the lyophilization vessel there were obtained 0.98 g of an amorphous torasemide modification; melting point (apparatus for melting point determination: Büchi 535): start of softening at about 80°C, decomposition at about 148°C.

The IR spectrum of the thus obtained sample corresponded to the IR spectrum of the new amorphous modification obtained in Example 1.

Example 5

A mixture (0.08 g) of crystal modifications I and II of torasemide prepared according to *Acta Cryst.* B**34** (1978) 1304-1310 was dissolved under stirring in 60 ml of demineralised water at a temperature of about 90°C within 10 hours, whereupon the solution was cooled to room temperature and filtered. Subsequently, the solution was frozen at a temperature of about -40°C and then the water was removed by lyophilization.

After isolation from the lyophilization vessel there were obtained 0.06 g of an amorphous torasemide modification; melting point (apparatus for melting point determination: Büchi 535): start of softening at about 80°C, decomposition at about 148°C.

The IR spectrum of the thus obtained sample corresponded to the IR spectrum of the new amorphous modification obtained in Example 1.

Example 6

A mixture (0.08 g) of crystal modifications II and III of torasemide prepared according to *Acta Cryst.* B34 (1978) 1304-1310 and HR patent application P980532A (US patent application 09/187046) was dissolved under stirring in 60 ml of demineralised water at a temperature of about 100°C within 5 hours, whereupon the solution was cooled to room temperature and filtered. Subsequently, the solution was frozen at a temperature of about -50°C and then the water was removed by lyophilization.

After isolation from the lyophilization vessel there were obtained 0.07 g of an amorphous torasemide modification; melting point (apparatus for melting point determination: Büchi 535): start of softening at about 80°C, decomposition at about 148°C.

The IR spectrum of the thus obtained sample corresponded to the IR spectrum of the new amorphous modification obtained in Example 1.

Example 7

A mixture (1.00 g) of crystal modifications I and III of torasemide prepared according to *Acta Cryst.* B34 (1978) 1304-1310 and HR patent application P980532A (US patent application 09/187046) was suspended in 50 ml of demineralised water at 5°C, 10 drops of an aqueous ammonia solution were added and then the solution was stirred at the same temperature for 18 hours, whereupon it was filtered. Subsequently, the solution was frozen at a temperature of about -60°C and then the water and ammonia were removed by the lyophilization.

After isolation from the lyophilization vessel there were obtained 0.98 g of an amorphous torasemide modification; melting point (apparatus for melting point determination: Büchi 535): start of softening at about 80°C, decomposition at about 148°C.

The IR spectrum of the thus obtained sample corresponded to the IR spectrum of the new amorphous modification obtained in Example 1.

Example 8

The amorphous torasemide modification (3.0 g) prepared according to Example 1 of the present invention was suspended in 60 ml of demineralised water at 25°C, 30 drops of an aqueous ammonia solution were added and the obtained solution was stirred at the same temperature for 30 minutes and then filtered. Subsequently, the solution was frozen at a temperature of about -30°C, whereupon the water and ammonia were removed by lyophilization.

After isolation from the lyophilization vessel there were obtained 2.94 g of an amorphous torasemide modification; melting point (apparatus for melting point determination: Büchi 535): start of softening at about 80°C, decomposition at about 148°C.

The IR spectrum of the thus obtained sample corresponded to the IR spectrum of the new amorphous modification obtained in Example 1.

Example 9

A mixture (1.20 g) of crystal modifications I, II and III of torasemide prepared according to *Acta Cryst.* B34 (1978) 1304-1310 and HR patent application P980532A (US patent application 09/187046) and of the amorphous torasemide modification prepared according to Example 1 of the present invention was suspended in 60 ml of demineralised water at 25 °C, 10 drops of an aqueous ammonia solution were added and the obtained solution was stirred at the same temperature for 30 minutes, whereupon it was filtered. Subsequently, the solution was frozen at a temperature of about -30°C and then the water and ammonia were removed by the lyophilization.

After isolation from the lyophilization vessel there were obtained 1.18 g of an amorphous torasemide modification; melting point (apparatus for melting point determination: Büchi 535): start of softening at about 80°C, decomposition at about 148°C.

The IR spectrum of the thus obtained sample corresponded to the IR spectrum of the new amorphous modification obtained in Example 1.

Example 10

The amorphous torasemide modification prepared according to Example 1 of the present invention was subjected to the test of the release of the active substance in water at a temperature of 37°C (USP 24) and the results are represented in Table 1.

Table 1: Release of the amorphous torasemide modification in water (USP 24) (37°C, 50 rpm, 1000 ml)

Time (minutes)	Released torasemide (%)
0	0
15	6.8
30	10.2
45	13.0
60	15.9
90	20.4
120	24.9

Claims

1. Amorphous torasemide modification characterized by the following data:
DSC: exothermic maximum at about 147°C (onset at about 144°C);
X-ray powder pattern (2 Θ): no diffraction maxima due to the amorphous nature;
IR characteristic absorption bands at 2900 to 3366 cm^{-1} and at 1400 to 1703 cm^{-1}.

2. Amorphous torasemide modification according to claim 1, characterized in that it is chemically pure.

3. Process for the preparation of the amorphous torasemide modification according to claim 1, characterized in that torasemide modifications are dissolved in water with or without the addition of a base at a temperature from 5°C to 100°C within 5 minutes to 24 hours and then the solutions are cooled to a temperature from -20°C to -70°C and water is removed.

4. Process for the preparation of the amorphous torasemide modification according to claim 3, characterized in that as the torasemide modifications crystal torasemide modifications I, II or III or an amorphous torasemide modification or any mixture of the crystal torasemide modifications I, II and II and of an amorphous torasemide modification are used.

5. Process for the preparation of the amorphous torasemide modification according to claim 3, characterized in that aqueous ammonia solution is used as the base.

6. Process for the preparation of the amorphous torasemide modification according to claim 3, characterized in that lyophilization is used as the method for the removal of the water and the base.

7. The amorphous torasemide modification according to claim 1, characterized in that it is used as a raw material for the preparation of pharmaceutically acceptable torasemide salts.

8. The amorphous torasemide modification according to claim 1, characterized in that, as a form of torasemide, it is used as a diuretic, as an agent for preventing heart or heart tissue damages caused by metabolic or ionic abnormalities associated with ischemia, in the treatment of thrombosis, angina pectoris, asthma, hypertension, nephroedema, pulmonary edema, primary and secondary aldosteronism, Bartter's syndrome, tumour, glaucoma, for decreasing intraocular pressure, acute or chronic bronchitis, in the treatment of cerebral edema caused by trauma, ischemia, concussion of the brain, metastases or epileptic attacks and in the treatment of nasal infections caused by allergens.

9. A pharmaceutical form, characterized in that, as the active ingredient, it contains an effective amount of the amorphous torasemide modification according to claim 1 without or, for that purpose, combined with one or more pharmaceutically acceptable additives such as sugar, starch, starch derivatives, cellulose, cellulose derivatives, mould release agents, and antiadhesive agents and possibly agents for flowability regulation.

10. A pharmaceutical form according to claim 9, characterized in that it is a tablet, a capsule or an injection.

Fig. 1: DSC of the amorphous torasemide modification

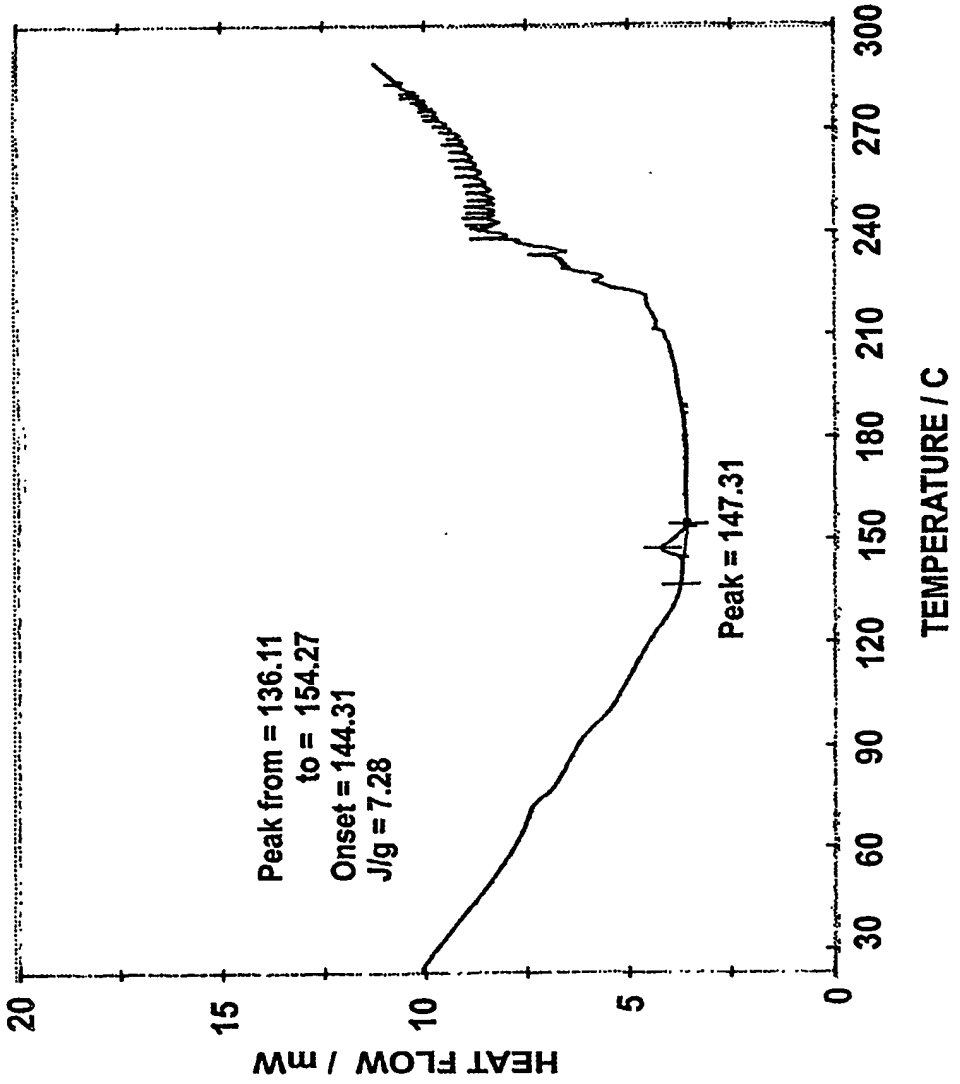


Fig. 2: X-ray powder pattern of a sample of the amorphous torasemide modification

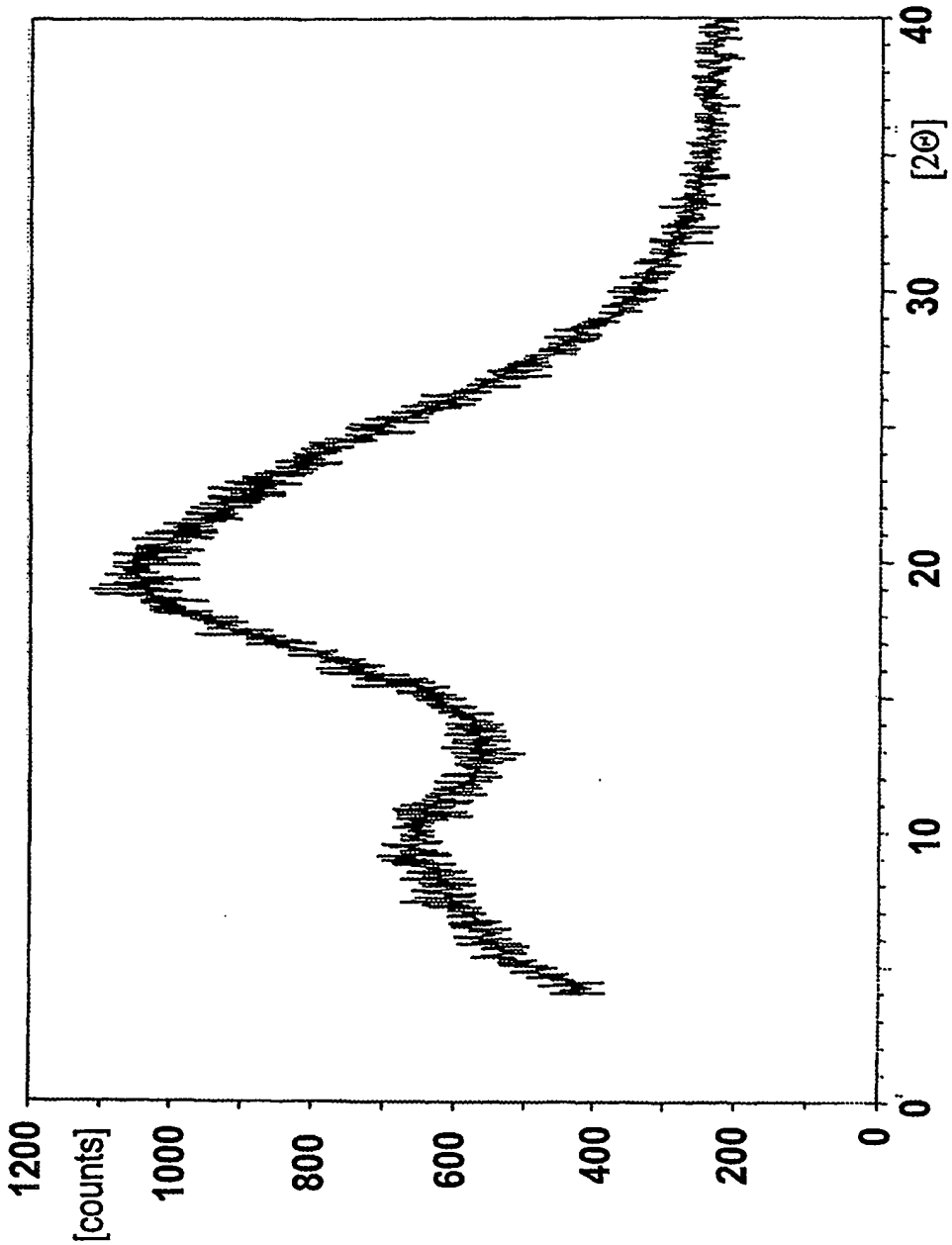
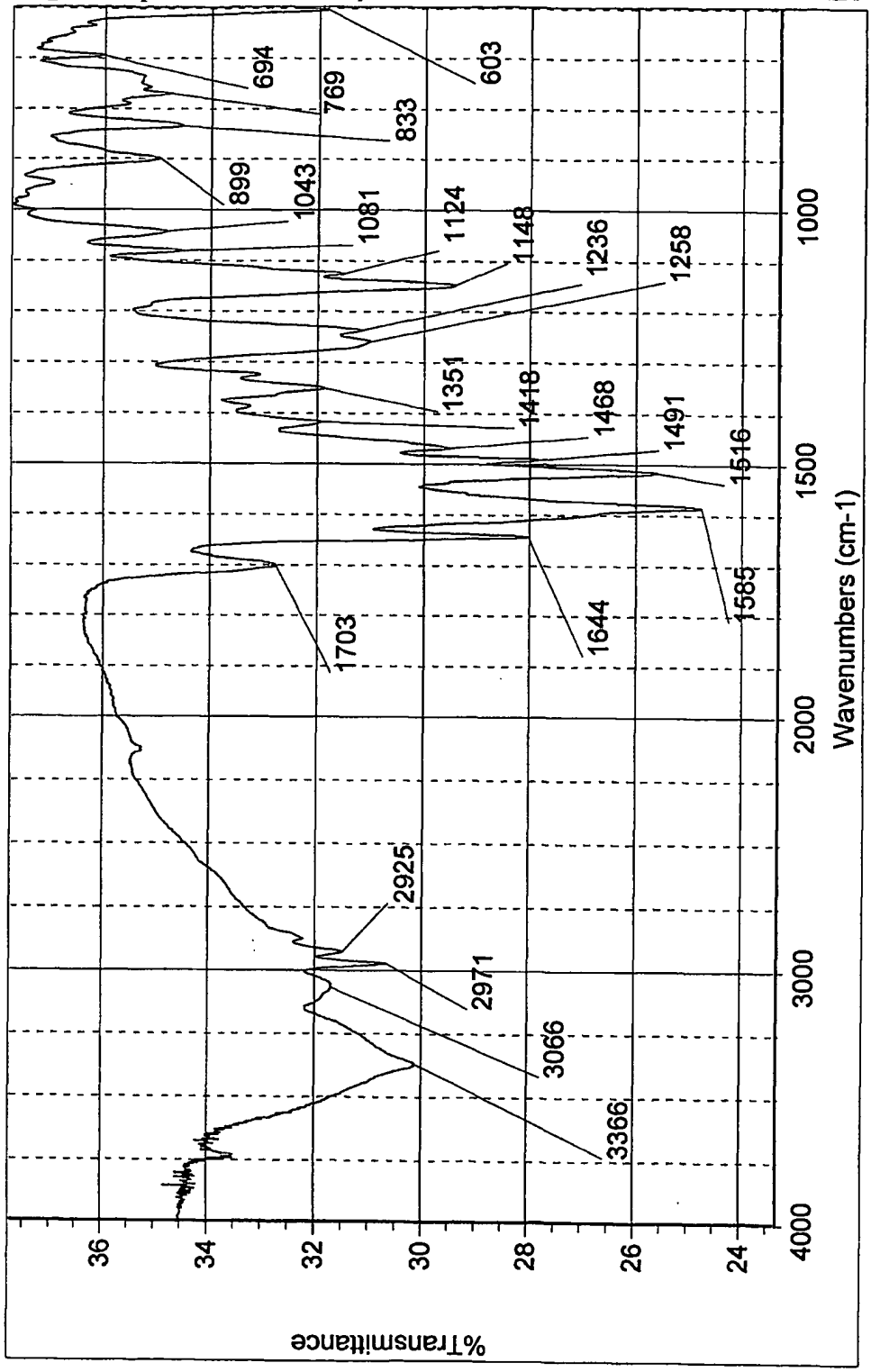


Fig. 3: IR spectrum of the amorphous torasemide modification recorded in KBr



INTERNATIONAL SEARCH REPORT

International Application No
PCT/HR 00/00011

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D213/74

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 00 20395 A (PLIVA, FARMACEUTSKA INDUSTRIJA,DIONICKO DRUSTVO) 13 April 2000 (2000-04-13) page 18 -page 23; claims 1-16	1-10
A	WO 96 26197 A (HOECHST JAPAN LIMITED) 29 August 1996 (1996-08-29) cited in the application page 18 -page 19; claims 1-9	1-10
A	DE 25 16 025 A (A. CHRISTIAENS S.A) 6 November 1975 (1975-11-06) cited in the application page 2 page 24; example 71	1-10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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26 January 2001	02/02/01

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

ational Application No
PCT/HR 00/00011

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 914 336 A (BRUNO DRECKMANN-BEHRENDT) 22 June 1999 (1999-06-22) column 2, line 4 - line 11	1-10
A	US 4 743 693 A (FRITZ TOPFMEIER ET AL.) 10 May 1988 (1988-05-10) the whole document	1-10
A	L. DUPONT ET AL.: "Structure Cristalline et Moléculaire d'un Diurétique Dérivé de l'Alkyl-1'(Phénylamino-4-pyridyl-3)sulfony l!-3 Urée: la Torasémide(C15H20N4SO3)" ACTA CRYSTALLOGRAPHICA, vol. B, no. 34, 1978, pages 1304-1310, XP002128455 cited in the application the whole document	1-10
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 8 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

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